Yescarta®

Kite Pharma's CAR T-Cell Therapy for Non-Hodgkin Lymphoma

Contributions of investigators from National Cancer Institute (NCI), NCI Technology Transfer Center's (TTC) facilitation of a cooperative research and development agreement (CRADA), and the subsequent collaboration between Kite Pharma and NCI investigators paved the way for FDA approval of Axicabtagene Ciloleucel (Yescarta®). NIH is solely responsible for the content of these materials.

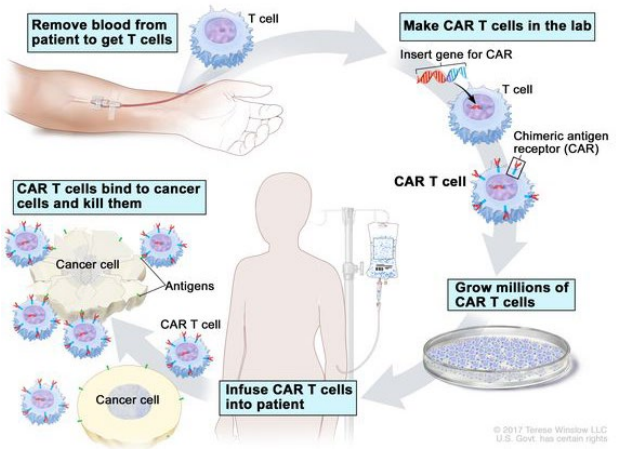
Discovery

NCI scientist Dr. Steven Rosenberg, often regarded as the father of cancer immunotherapy, began working on immunotherapy in the 1970s when little was known about T lymphocyte function in cancer. In the late 1980s, Dr. Rosenberg began collaborating with Dr. Zelig Eshhar on advancing the usage of T cells as immunotherapy, specifically the use of chimeric antigen receptor (CAR) T cells. This collaboration resulted in multiple patent filings, including applications, which later issued as foundational patents in the CAR T space. In 2007, Dr. Rosenberg and Dr. James Kochenderfer, a medical oncology/hematology fellow at NCI, began working together and focused on the anti-CD19 CAR. They constructed two CARs containing a mouse-anti-human-CD19 antibody chain derived from the FMC63 hybridoma. In 2009, they went on to use one of their constructed CD19 CARs (the same CAR used in axicabtagene ciloleucel) to treat the first patient with autologous CAR T-cells.

Role and Impact of Tech Transfer

Despite demonstrating significant clinical success, there were inherent challenges with manufacturing CAR T cells at scale. After isolating T cells from a patient, the cells are genetically modified and expanded, and then introduced back into the body via transfusion. To make this drug a reality, NCI scientists needed the backing of a partner to provide expertise on commercial scale manufacturing and to help finance this expensive process. Many pharmaceutical companies were dissuaded by the laborious, time intensive, and costly process to manufacture CAR T cells. However, Dr. Arie Belldegrun, a former research fellow for Dr. Rosenberg and founder of Kite Pharma, visited Dr. Roseneberg's lab in 2010 and was encouraged when he saw some scans of the first patient treated with what would later become axicabtagene ciloleucel.

Over the next 2 years, TTC worked out a deal with Kite Pharma. TTC created a contractual framework of collaboration between NCI scientists and Kite Pharma through two CRADAs, which proved essential for the successful commercialization of axicabtagene ciloleucel. The CRADAs provided a framework for collaboration between the two parties helping to contribute to three important pieces of intellectual property that underlie



CAR T-Cell Therapy Lab Concept Image Source: NCI

axicabtagene ciloleucel: ways to produce T cells to treat B-cell cancers, ways to condition patients so that their bodies can better accept T-cell therapy, and ways to identify treatment candidates.

The symbiotic relationship between NCI and Kite Pharma enabled the successful commercialization of axicabtagene ciloleucel. Together, they worked within the CRADAs to make the drug a reality, each bringing something to the table. NCI brought the research and clinical contributions, whereas Kite contributed critical expertise that enabled commercial scale manufacturing and financial capital that enabled significant research and testing efforts.

In 2017, axicabtagene ciloleucel became the first CAR T-cell therapy approved by FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma. Axicabtagene ciloleucel is giving new life to lymphoma patients who otherwise had no treatment options. In ZUMA-7, a global, multicenter, single-arm, open label Phase 2 study that evaluated axicabtagene ciloleucel in patients with relapsed or refractory indolent NHL after at least two prior lines of therapy, it was demonstrated that, of all treated patients, 92% had an overall response rate with a 75% complete response.

Beyond the significant clinical benefits that the therapy has provided, axicabtagene ciloleucel's successes have also had far-reaching impacts for the adoptive cell therapy discipline as a whole. The successful commercialization of axicabtagene ciloleucel substantially decreased the perceived risk of adoptive cell therapy by demonstrating that it works. This has resulted in an an explosive growth of research and development within the space as companies continue to multiply and develop adoptive cell therapies for various indications.